SUPPORT NEEDED TO ESTABLISH NONPROFIT ORGANIZATION TO ADDRESS THE 3Rs

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ABSTRACT

Every year in the U.S. tens of millions of animals are used and killed in experiments to test industrial chemicals, drugs, pesticides, cosmetics, food additives, and many other products. However, using animals to understand human biology often fails, resulting in mild to severe adverse reactions, and even death. The scientific value of animal experiments at the regulatory level has been in question for more than a decade. In 2007 the National Academy of Sciences, through the National Research Council, published a groundbreaking report titled *Toxicity Testing in the 21st Century: A Vision and Strategy*, in which they state that the goal of toxicity testing should be to move away from the current animal-based approach and toward modern, non-animal testing methods in the quest for better public health. This Capstone explores the strengths and weakness of establishing a nonprofit organization with the sole function of collaborating with scientists and organizations across the life sciences from industry, academia, funders, and regulatory authorities to address the aforementioned issues. The goal is to help manifest the 3Rs vision (to reduce, replace, and refine animal use) in the U.S., bringing the number of animals used in toxicological experiments down while improving public health. The author recommends the establishment of a nonprofit organization because momentum is needed to address the public health ramifications of continued reliance on animal experiments and the time is now to tackle the problem of unreliable testing. Paul Weinstein reviewed this paper.

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For Kenny, who has been patient, supportive, and instrumental not only in the creation of this Capstone but in everything I endeavor.

And for Rihana, who has been gracious in forgoing our long walks in the woods every Sunday as I have pursued this degree.

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Action Forcing Event

On January 15, 2016, the *New York Times* reported on a drug trial in France in which six healthy men were hospitalized--one brain-dead and four others seriously injured--while participating in a clinical drug trial.[1] The French health minister was surprised by the adverse effects of the drug and said, "the drug had previously been tested on animals, including chimpanzees" -- our closest living relatives. The drug, which was intended to alleviate neurodegenerative diseases, as well as help with mood and anxiety, was given to 90 healthy volunteers as part of an initial clinical trail.[2] Incidents like these illuminate the statistic that up to 96 percent of drugs fail in human trials after being tested on animals.[3] In fact, the failure rate is rising; it was 86 percent in 1985, 92 percent in 2003, and 96 percent in 2012 (the most recent year with complete data).[4] Evidence continues to mount that using animals to understand human responses to drugs, chemicals, and other products do not provide the most accurate public health information. There is a strong correlation between the failures of animal studies and

[1] Sewell Chan, "6 Hospitalized, One of Them Brain-Dead, After Drug Trial in France," New York Times, 2016, http://www.nytimes.com/2016/01/16/world/europe/french-drug-trialhospitalization.html?_r=1.
[2] Ibid.
[3] John Pippin, "Animal Research in Medical Sciences: Seeking a Convergence of Science, Medicine, and Animal Law." South Texas Law Review, 2013;54(3):469-511.
[4] Ibid.

harmful consequences for the human population.[5] The inverse is also true: non-animal testing methods and strategies are proving to be more effective in predicting human responses, leading to better public health outcomes.

Statement of the Problem

Every year in the U.S. tens of millions of animals are used in experiments to test industrial chemicals, drugs, pesticides, cosmetics, food additives, and many other products.[6] However, using animals to understand human biology often fails, resulting in mild to severe adverse reactions, and even death. For example, according to a 2014 FDA report, adverse drug reactions cause about 100,000 deaths annually and are the 4th leading cause of death in the U.S. These deaths occur *after* extensive animal studies have been conducted.[7] There is also the problem that misleading animal experiments cause scientists to pass up drugs or cures that do not work in animals but *could* be effective in treating human conditions. Of course, it is hard to know how many potential cures or treatments would have been suitable for humans that never made it to market because they failed in animal experiments, but there are numerous examples of scientists questioning animal-based results. Aysha Akhtar, MD, MPH, double-board certified neurologist and preventive medicine/public health specialist writes, "An

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5 John Pippin and Kristie Sullivan, "Dangerous Medicine: Examples of Animal-Based "Safety" Tests Gone Wrong," Physicians Committee for Responsible Medicine, 2016, http://www.pcrm.org/research/animaltestalt/animaltesting/dangerous-medicine-examples-of-animal-based-tests.

[6] Animal Legal Defense Fund, "Animal Testing and the Law," 2014, http://aldf.org/resources/when-you-witness-animal-cruelty/animal-testing-and-the-law/.

[7] Food and Drug Administration, "Preventable Adverse Drug Reactions: A Focus on Drug Interactions," 2014, www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm110632.htm.

editorial in *Nature Reviews Drug Discovery* describes how tamoxifen, one of our most effective drugs against certain types of breast cancer, would have been abandoned because it causes liver tumors in rats, a problem that does not carry over to humans."[8] There is also the case of Aspirin. Aspirin is one of the most widely used drugs in the world and has been on the market for over 100 years. It is used at almost all life stages and gestational periods, yet if it were developed today it would not come to market because in almost every animal-based toxicological experiment it kills animals and fails to alleviate pain as it does for humans.[9] The only reason humans use it today is because it was discovered in 1899 before the field of regulatory toxicology was developed.

The scientific value of animal experiments at the regulatory level has been in question for quite some time and in 2007 the National Academy of Sciences (NAS) through the National Research Council published a groundbreaking report titled *Toxicity Testing in the 21st Century: A Vision and Strategy* (TT21C) in which they state that the goal of toxicity testing should be to move away from the current animal-based approach and toward modern, non-animal testing methods in the quest for better public health.[10] The Environmental Protection Agency commissioned this report because it and many other scientific bodies recognized the inherent scientific shortfalls with using animals. This report created a worldwide shift in the field of toxicology encouraging scientists to develop new methods and strategies to assess chemicals and allowed scientists to be more vocal and honest about the scientific problems with animal experiments.

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[8] Nature Editorial, "Follow the Yellow Brick Road," Nature Reviews, Drug Discovery, Volume 2, 2003.
[9] Thomas Hartung, "Per Aspirin Ad Astra…," Alternatives to Laboratory Animals, 2009.
[10] National Research Council, "Toxicity Testing in the 21st Century: A Vision and Strategy," National Academy of Sciences, 2007, http://www.nap.edu/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a.

History

A better understanding of toxicology, and its history, is necessary in understanding the policy problem at play. The goal of toxicology is to understand the adverse effects of chemicals on living organisms. The term "chemical" is used here in its truest form, meaning any building block (natural or synthetic) that occurs in the environment or in human-made products. The "Father of Toxicology," Mathieu J. B. Orfila, published a book in 1813 which detailed the symptoms of poisons, but the field did not make additional significant advances until the 20th century.[11] In 1927 a British toxicologist developed one of the most commonly used toxicological experiments, the Lethal Dose 50 (LD_{50}) test. The LD_{50} test is the dose at which 50 percent of the animals die after being fed, injected, or otherwise given the chemical. The test is slow and painful, and animals are not given pain relief.[12] This test was used for decades as the worldwide standard in toxicological experiments. Regulatory toxicology was formalized in the U.S when the Food and Drug Administration was established in 1938. There were a number of tragedies that led to the formation of the FDA but one of them was the Lash Lure incident in which more than a dozen women were blinded, and one died after using untested mascara with coal tar in the early 1930s.[13] Today, the FDA regulates products such as cosmetics, drugs, medical devices, and as of 2009, tobacco products.

[11] Juliana DeCarvalho Anderson, "Toxicology Timeline," Toxipedia, 2012, http://www.toxipedia.org/display/toxipedia/Toxicology+Timeline.
[12] Science Museum, "Medium Lethal Dose (LD50)," http://www.sciencemuseum.org.uk/broughttolife/techniques/ld50.
[13] Food and Drug Administration, "FDA History - Part II. The 1938 Food, Drug, and Cosmetic Act," 2012, http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm054826.htm.

Because of the FDA's formation, health cases and incidents for FDA regulated products declined.[14]

No major advancements in the field of toxicology were made after the LD_{50} test was developed until 1944 when John Draize, a FDA scientist, developed a testing method to look at the acute (or short-term) effects of chemicals – primarily cosmetics – in response to the Lash Lure case. The method, which is still widely used today, involves albino rabbits, although other species, including dogs, are used. There are two Draize protocols; one for the skin and the other for the eye. Both protocols assess how much of an "irritant" or how "corrosive" an ingredient or product is.[15] The skin test involves restraining live animals, shaving their backs, and applying a chemical for several hours (depending on the study duration). The chemical is then removed and the state of injury is recorded based on a subjective rating system by the experimenters after a period of hours/days/weeks, if the animal has not died from the trauma. The eye test is similar: the animal is restrained, the eye is held open, and the chemical is administered. Rabbits are usually chosen because they do not have tear ducts, so they cannot flush the chemical out. Again, if the animal survives, the state of injury is recorded based on what the experimenter sees on a 3-point scale. The animals are either killed and have their organs dissected, or they are reused in another experiment. It should be noted that anesthesia is almost never given in all toxicological tests because experimenters say it

[14] Wallace Janssen, "The Story of the Laws Behind the Labels," Food and Drug Administration, 1981, ww.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm056044.htm

[15] Ana Gallegos Saliner and Andrew Worth, "Testing Strategies for the Prediction of Skin and Eye Irritation and Corrosion for Regulatory Purposes," European Commission Directorate General Joint Research Centre, 2007, https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/doc/EUR_22881_EN.pdf.

can potentially interfere with the findings. Like the LD_{50} test, the Draize protocol has been one of the most commonly used toxicological experiments worldwide. However, because of the TT21C report in 2007, many in the scientific community are beginning to question the utility of this protocol, not because of the ethical implications but because the scoring system is subjective and animal skin and eyes differ significantly from humans – e.g. humans do have tear ducts and the structure of human and rabbit corneas differ.[16]

In recent decades the Organization for Economic Co-operation and Development (OECD) has been a clearinghouse for testing protocols. The OECD develops test guidelines and hosts a number of programs that allow member countries (and aspiring countries) to participate and create agreed upon standards and methods. Historically OECD's testing-related programs relied heavily on animal experiments (as did the field of toxicology at large), but there's been a slow shift in the last 15 years. The shift is due, in part, to two reasons. The first is that an international coalition of animal protection organizations called the International Council on Animal Protection in OECD Programmes (ICAPO), which formed in 2002. was granted status as "invited experts" due to their scientific credibility. ICAPO has pushed member countries to be more accepting of non-animal testing methods and strategies. ICAPO's success comes from working directly at the OECD by submitting comments, inviting experts to meetings, and participating in working groups. ICAPO also ensures that OECD countries abide by their treaty obligations under the "Mutual Acceptance of Data" to accept data from approved

[16] American Anti-Vivisection Society, "Animals in Science," 2016, http://aavs.org/animals-science/how-animals-are-used/testing/.

test guidelines instead of conducting duplicative animal tests.[17] Secondly, the scientific community at large is realizing how non-animal testing methods are better predictors of human health outcomes. This realization has been fueled by progressive legislation in the European Union banning the use of animals in cosmetic experiments and limiting animal experiments for chemicals.[18] Because of these laws banning or limiting the use of animals in experiments (which have been created because of public pressure) scientists have been forced to develop non-animal testing methods. These more effective testing methods are now being used worldwide.

Many toxicologists today believe that a limited amount of animal testing is necessary but that alternative testing methods are more predictive in assessing adverse effects in humans. The number of scientists who believe that non-animal testing approaches are the best way to understand toxicity in humans is growing, and it is largely because of the aforementioned landmark report published by the National Academy of Sciences in 2007, *Toxicity Testing in the Twenty-First Century: A Vision and A Strategy* (TT21C).[19] They note that toxicity testing is often performed on animals, including rabbits, rats, mice, dogs, cats, primates, hamsters, guinea pigs, birds, and fish, exposing animals to chemicals at doses up to 1,000 times higher than humans would

[17] International Council for Animal Protection in OECD Programmes, "About Us," 2016, http://www.icapo.org/.
[18] European Commission, "Ban on Animal Testing," 2016, http://ec.europa.eu/growth/sectors/cosmetics/animal-testing/index_en.htm.
[19] National Research Council, "Toxicity Testing in the 21st Century: A Vision and a Strategy," The National Academies Press, 2007, http://www.nap.edu/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a.

ever be exposed.[20] Some tests are required by government agencies such as the Environmental Protection Agency (EPA) before a company can market a product. Generally, however, there are not many requirements written into the regulations that mandate animal testing. The FDA does not have a list of prescriptive tests for the regulation of drugs and medical devices; rather, the FDA asks industry to provide whatever data they deem necessary in understanding how the drug or device is safe and effective. In order to speed through the regulatory process, pharmaceutical companies "front-load" data (almost exclusively animal-based data) so that the drug can begin the clinical trial process and get to market as quickly as possible.[21]

In order to translate the results of animal tests, scientists and regulators assume that the biological processes of animals and humans are similar. However, this is often incorrect. There are some basic biological functions that all animals share, whether human or non-human; however, the details about how each species absorb, metabolize, and excrete chemicals vary widely.[22] Species differences and high testing doses make it difficult for scientists to fully understand what is going on in the human body. These basic translational problems often lead to more animal testing, and worse yet, delaying appropriate chemical regulations. Testing on animals is also costly and time consuming.

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[20] Chris Kent, "Basics of Toxicology," Intelligent Communications and The Partnership for Environmental Technology Education, 1998, https://books.google.com/books?id=VEUlWz4vQssC&pg=PA66&lpg=PA66&dq=doses+100+1000+animal+tox&source=bl&ots=0rfHhRVf0T&sig=Q2bvQ6hop8TaRcEM9GZobiRfWiI&hl=en&sa=X&ei=TAAzVfvWHcKcNo6ZgYAK&ved=0CEoQ6AEwCQ#v=onepage&q=doses%20100%201000%20animal%20tox&f=false.

[21] Food and Drug Administration, "New Drug Application," 2015, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/.

[22] Physicians Committee for Responsible Medicine, "Chemical Safety Basics," http://www.pcrm.org/research/animaltestalt/chemtesting/chemical-testing-basics-toxicity-testing

A series of tests on one chemical can cost upwards of $10 million and can take approximately three years to plan, conduct, and summarize.[23] Because of these factors, toxicity assessment needs are outpacing the capacity of testing laboratories.

What these problems ultimately led to was the EPA commissioning the NAS to develop the TT21C report because there were too many chemicals to review and not enough resources (time, money, laboratories) to use traditional, animal-based methods. The EPA asked the National Research Council to consider current limitations and to provide a framework to adequately protect human health and the environment. The outcome was a recommendation to move away from animal-based models and toward human-relevant approaches and technologies. The TT21C report lays out specific steps to modernize toxicity testing. They begin by stating that a research effort will be needed to "develop, assess, and implement non-animal methods."[24] The authors envisioned that this would be accomplished in phases, beginning with clarifying toxicity pathways and then developing relevant databases. This information would then be used to develop tests that tackle specific elements of toxicity. These tests would then be assessed for relevance to humans and used instead of animals. Efforts like these are already underway in several areas of the federal government, such as the EPA, and the National Center for Advancing Translational Science, one of the Institutes at the National Institutes of Health.

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[23] Meredith Kohn, "Alternative to Animal Testing Gaining Ground," The Baltimore Sun, 2010, http://articles.baltimoresun.com/2010-08-26/health/bs-hs-animal-testing-20100826_1_animal-testing-animal-welfare-act-researchers.

[24] Physicians Committee for Responsible Medicine, "Frequently Asked Questions About Chemical Regulation," http://www.pcrm.org/research/animaltestalt/chemtesting/faq-chemical-regulation.

This shift in thinking began because the EPA commissioned the National Research Council to address the inherent pitfalls of animal-based toxicology. The report legitimized the concept that using animals in toxicity tests should be phased out over a period of time as alternative methods are developed, and that the future of testing will rely on non-animal methods. Most toxicity tests occur for regulatory purposes under the EPA and FDA and both agencies have signed a Memorandum of Understanding agreeing to harness the spirit of TT21C and fold it into their existing work, signaling one of the biggest shifts in toxicology and toxicological policy in decades.[25]

Background

State of Play

The policy discussion around the use of animals in toxicity testing would be incomplete without a look at some of the alternative, non-animal testing methods available. Most modern testing methods fall into three categories: *in vitro*, *in silico*, and microfluidics. *In vitro* methods utilize cells and tissues both from humans and non-humans to test compounds at the molecular level. *In vitro* tests can rapidly screen or assess thousands of chemicals because they can be automated and done robotically. High throughput screening is already happening in the pharmaceutical industry to assess if a drug will make it to the next stage of the drug development process.[26] High throughput screening is also being used effectively at the chemical and cosmetic level. The National Center for Advancing Translational Science (NCATS) is the government

[25] Memorandum of Understanding on High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings, 2010, http://www.niehs.nih.gov/about/highlights/assets/docs/memorandum_of_understanding_2010_508.pdf.
[26] Scripps Florida, "High Throughput Screening (HTS)," 2016, https://www.scripps.edu/florida/technologies/hts/.

powerhouse for this type of work.[27] *In vitro* assays work hand-in-hand with high throughput screening and the outcomes are already proving to be successful.[28] The authors of the TT21C report predicted this in 2007 when they said, "This report envisions a not-so-distant future in which virtually all routine toxicity testing would be conducted in human cells or cell lines *in vitro* by evaluating perturbations of cellular responses in a suite of toxicity pathway assays using high throughput robotic-assisted methodologies."[29]

In silico methods, or computational models, are getting more sophisticated by the year. *In silico* models are currently being used as "non-testing" methods to get information on chemicals. Many models are available but one that is currently being used at the regulatory level is "read across," in which chemicals that share similar structures are grouped together. This gives scientists information on chemicals that may not have extensive data profiles.[30] For example, chemical A and B are structurally similar (which allows scientists to know that they will react similarly in the human body), but chemical A only has skin irritation data and chemical B only has eye irritation data. Once toxicologists put both chemicals and the existing data in their software they are able to "read across" and determine that the missing tests do not need to be conducted for the other chemical. See the chart below from the European Union Reference Laboratory for Alternatives to Animal Testing to further understand this concept.

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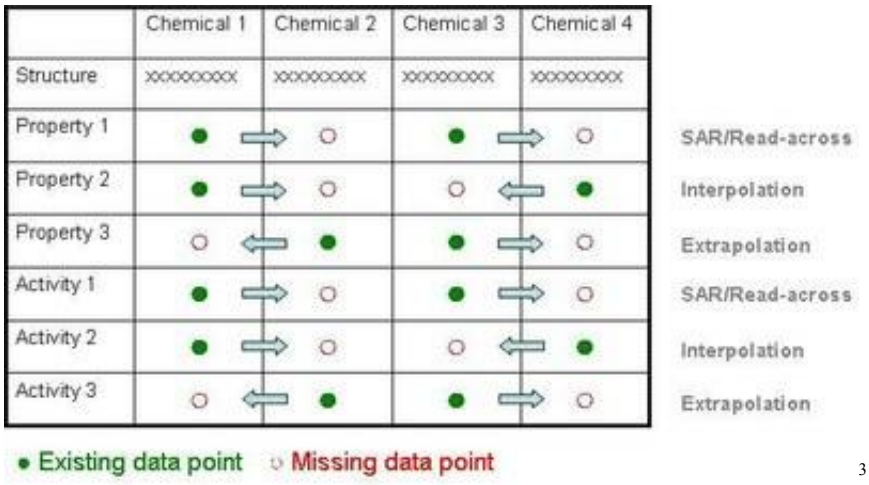
[27] National Center for Advancing Translational Sciences, 2016, https://ncats.nih.gov/.
[28] S Fox et al., "High-throughput screening: updates on practices and success," Journal of Biomedical Screening, 2006, http://www.ncbi.nlm.nih.gov/pubmed/16973922.
[29] National Research Council, "Toxicity Testing in the 21st Century: A Vision and Strategy," National Academy of Sciences, 2007, http://www.nap.edu/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a.
[30] Cosmos, "*In Silico* Predictions of Toxicity,"http://www.cosmostox.eu/what/predictions/.



[31]

In silico models allow scientists to minimize duplicative or "unnecessary" testing, but as these models get more predictive they are developing virtual organs and cells that can simulate what might happen to a chemical in the human body before ever going through an animal or human body.[32]

Microfluidics is one of the most exciting and promising non-animal testing methods because there is so much potential for application across industries. Microfluidics, or microphysiciological systems (commonly known as human/organs-on-a-chip), is an interdisciplinary field that combines biology, toxicology, engineering, physics, chemistry, nanotechonolgy, tissue engineering, and biotechnology to develop models of human biology. Several organs-on-a-chip are currently available for use, such as the lung, heart, gut, and bone marrow. These organ systems are the size of a thumb

[31] European Union Reference Laboratory for Alternatives to Animal Testing, "Chemical Categories and Read-Across," 2016, https://eurl-ecvam.jrc.ec.europa.eu/laboratories-research/predictive_toxicology/background/chemical-categories-and-read-across.
[32] Hannah Raunio, "*In Silico* Toxicology – Non-testing Methods," Frontiers in Pharmacology, 2011, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3129017/.

drive and are based on cells from humans.[33] The Wyss Institute at Harvard University is leading the field and their successful completion of the "lung-on-a-chip" was one of the first organ systems created.[34] This 3-D system takes cells from human blood vessels and lungs and mimics the functions of the living lung. It even "breathes"-- see the footnote for a four-minute video of how this technology works.[35] The ultimate goal is for all the organ microfluidic devices to work together as a mimic of the human body. Medicine and potential adverse outcomes can then be personalized to the individual. The Defense Advanced Research Projects Agency, NIH, and FDA have all invested heavily in microfluidic technology to date.[36]

Application of these human-relevant testing methods will likely be seen in the chemicals sector where major legislative efforts have been underway to reform the nearing 40-year old Toxic Substances Control Act (TSCA), the only major environmental statute never substantially updated since its inception.[37] Environmentalists and industry both claim TSCA is "broken," though for different reasons. Environmentalists believe it allows dangerous chemicals on the market and in the environment.[38] Industry is frustrated by the various state regulations, which have created a patchwork of policies difficult to abide by and sell products in.[39] Environmental groups have created public

[33] Wyss Institute, "Organs-on-Chips," http://wyss.harvard.edu/viewpage/461/.
[34] Eric W. Esch and Anthony Bahinski, "Organs-on-Chips at the frontiers of drug discovery," Nature Reviews Drug Discovery, 2015, http://www.nature.com/nrd/journal/v14/n4/fig_tab/nrd4539_F1.html.
[35] Wyss Institute, "Lung-on-a-chip," http://wyss.harvard.edu/viewpage/240/.
[36] DARPA, "DARPA and NIH to fund 'human body on a chip' research," MIT News, 2012, http://news.mit.edu/2012/human-body-on-a-chip-research-funding-0724.
[37] Environmental Defense Fund, "Chemicals policy reform," 2016, https://www.edf.org/health/policy/chemicals-policy-reform.
[38] Natural Resources Defense Council, "Take Out Toxics,"http://www.nrdc.org/health/toxics.asp.
[39] American Chemistry Council, "TSCA Modernization," 2016, https://www.americanchemistry.com/Policy/Chemical-Safety/TSCA.

campaigns to reform TSCA and have negatively impacted the chemical industry's image. In every congressional session since 2005 a bill has been introduced to address the issue but they have all failed to gain momentum until 2015. In 2015 a major breakthrough was made when both the House and Senate passed bipartisan bills to reform the statute that regulates the tens of thousands of industrial chemicals on the market. The House passed a slim bill, which only addressed a few key problems with TSCA (confidential business information and preemption, most notably) in June of 2015 by a vote of 398-1.[40] The Senate passed a more comprehensive bill by unanimous consent in December of that same year.[41] The Senate bill takes into consideration many toxicological principles mentioned in the TT21C report and captures those key points in the spirit of the whole bill. The House bill does not address toxicological issues, preferring the status quo. The conferencing process is currently underway so the final package is yet to be determined but this will be the first re-write of a major piece of legislation that will impact the field of toxicology.

Key Players

A number of influential groups and individuals have been advocating to reform TSCA, and most have fairly large budgets. They include: Congress (Senator Booker has been a key champion in the TSCA reform process), environmental organizations, American Chemistry Council, EPA, OECD, European Commission (home to the European Union Reference Laboratory for Alternatives to Animal Testing), The National Centre for

[40] Cristina Marcos, "House passes chemical safety reform bill," The Hill, 2015, http://thehill.com/blogs/floor-action/house/245913-house-passes-chemical-safety-reform-bill.
[41] Timothy Cama, "Senate passes overhaul of chemical safety rules," The Hill, 2015, http://thehill.com/policy/energy-environment/263680-senate-passes-chemical-safety-reform.

the Replacement Refinement & Reduction of Animals in Research, FDA, Personal Care Products Council, National Association for Biomedical Research, Pharmaceutical Research and Manufacturers of America, and the animal protection community**.**

The ramifications of TSCA reform cannot be overstated. The debate been ongoing for many decades and it involves a multibillion dollar industry, as well as stakeholders from various sectors and nonprofit organizations and, of course, EPA at large. Lastly, TSCA reform requires Congressional action, so both the House and Senate have been involved in chemical reform discussions at every level. For the purposes of animal testing, the key champion has been Senator Cory Booker (D-NJ). In hearings and press conferences he has mentioned his own ethical motivations for supporting the issue, as well as his desire to ensure human-relevant testing methods are in place. As one of the Environment and Public Works committee members he was influential in inserting language into the bill that eventually passed the Senate, ensuring that non-animal testing methods are used first, and preferentially, before animal-based methods are adopted. As one of just a few vegan Members of Congress, and the only vegan Senator, he tweets about his beliefs regularly.[42] He has also introduced many animal-friendly bills with the Humane Society Legislative Fund.[43]

Being a progressive, Senator Booker has also been courted by many environmental organizations to champion issues with respect to chemical reform. The Environmental Defense Fund, Environmental Working Group, and Natural Resources

[42] Cory Booker, Twitter, 2016, https://twitter.com/CoryBooker/status/702338206256070656.
[43] Humane Society Legislative Fund, "Humane Society Legislative Fund Endorses Sen. Cory Booker of New Jersey for Re-Election to U.S. Senate," 2014, http://www.hslf.org/news/press-releases/booker-endorsement-2014.html.

Defense Council were the initial catalysts for federal chemical reform. They believe that there is not enough data on chemicals and the public needs to know which chemicals are safe and which are not. While environmental organizations recognize that there are some shortfalls with animal derived data, they are united in the belief that there should be no limits on the types of animal experiments EPA or industry can request or conduct. They want as much data as possible and are not deterred by the translational issues or ethics. They believe it is a worthy sacrifice to use animals in a laboratory setting in order to gain protections for humans and the environment. Most environmental organizations that engage on chemicals, cosmetics, and pesticides are motivated by the human health ramifications more so than the environment – see footnotes for explanations on their website as to why.[44] [45] [46] They are a well-funded group of organizations with collectively over $350 million. Surprisingly, one of the biggest opponents animal protection advocates face in the TSCA reform discussion is not industry, but rather the environmental organizations because they do not want to limit any kind of data that could be generated.

The American Chemistry Council (ACC) is the largest chemical industry trade group, representing almost all the large chemical-based corporations. Many Republican Members of Congress have a close relationship with ACC based on their contributions to political candidates and the nature of the issue. They are very active on the Hill as their $10+ million lobbying budget suggests, and since the GOP controls both the House and

[44] Environmental Defense Fund, "Our finances," 2016, https://www.edf.org/finances.
[45] Natural Resources Defense Council, "About NRDC: Finances," 2016, http://www.nrdc.org/about/finances.asp.
[46] Charity Navigator, "Environmental Working Group," 2016, http://www.charitynavigator.org/index.cfm?bay=search.summary&orgid=8564#.Vty1nRjURSs.

Senate, ACC reviews all issues other stakeholders bring forth with respect to chemicals.[47] ACC and EPA have a complicated relationship as one might expect due to the fact that EPA regulates ACC companies.

EPA is a government agency in charge of protecting human health and the environment. It implements TSCA and regulates a number of industries that test on a great number of animals, such as the pesticides industry. EPA requests, requires, and conducts a lot of animal experiments although they are also the most progressive of all the government agencies that engage in animal experiments. EPA has funded and supported the development and use of non-animal testing methods.[48] EPA has stated what alternative methods it is willing to accept and which are not and why. Its employees attend workshops put on by the animal protection community and it has many public policies about the institutional desire to reduce animal experiments.[49] The Agency believes that animal experiments are necessary in certain instances but it couples that with the institutional desire to move toward more human-relevant testing methods in the long run. EPA commissioned TT21C report because it saw the limitations of animal experiments and wanted to know if there was a better way to assess chemical risk.

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[47] OpenSecrets.org, "American Chemistry Council," The Center for Responsive Politics, 2016, https://www.opensecrets.org/lobby/clientsum.php?id=D000000365.

[48] Unilever and Environmental Protection Agency, "U.S. EPA and Unilever Announce Major New Research Collaboration to Advance Non-Animal Approaches for Chemical Risk Assessment," Business Wire, 2015, http://www.businesswire.com/news/home/20150908005307/en/U.S.-EPA-Unilever-Announce-Major-Research-Collaboration.

[49] United States Environmental Protection Agency, "EPA's Updated Science Policy on Testing Antimicrobial Cleaning Products for Eye Irritation Will Further Reduce Animal Testing," 2015, https://www.epa.gov/pesticides/epas-updated-science-policy-testing-antimicrobial-cleaning-products-eye-irritation-will.

EPA is an active participant in the OECD process and assists the OECD in helping it to create test guidelines for toxicology. OECD's mission is to "promote policies that will improve the economic and social well-being of people around the world."[50] Its testing-related activity spans many issues from nanotechnology, to chemicals, to pharmaceuticals. Notably, it conducts validation studies. OECD validates test methods to see if they are fit for use across broad applications and in 2005 member countries adopted a guidance document that provides principles and criteria for non-animal validation studies, harmonizing the various approaches taken by countries around the world.[51] The European Union Reference Laboratory for Alternatives to Animal Testing (EURL ECVAM) is the most widely recognized scientific body that works to validate studies and has a progressive outlook on the issue. Often OECD and EURL ECVAM will work closely together on studies. EURL ECVAM was formally established in 2011 to "promote the development and dissemination of alternative methods and approaches, their application in industry and their acceptance by regulators." However, validation studies have been conducted by ECVAM since 1991 under the European Commission Directive 86/609/EEC.[52]

The National Centre for the Replacement Refinement & Reduction of Animals in Research (NC3Rs) is a UK based public-private partnership that is dedicated to reducing, replacing and refining the use of animals in laboratories (the "3R's"). NC3Rs is a scientific body that works with scientists, companies, universities, regulatory bodies,

[50] The Organisation for Economic Co-operation and Development, 2016, http://www.oecd.org/about/.
[51] The Organisation for Economic Co-operation and Development, "Animal Welfare," 2016, http://www.oecd.org/chemicalsafety/testing/animal-welfare.htm
[52] European Union Reference Laboratory for Alternatives to Animal Testing, 2016, https://eurl-ecvam.jrc.ec.europa.eu/.

and nonprofit organizations across sectors. It also works nationally and internationally to fund research that fits the 3Rs mission, as well as innovating the field. NC3Rs also engages on policy and regulation reforms and helps to commercialize novel testing methods and strategies. It "provides an evidence base for changes in policy, practice and regulation through data sharing and knowledge exchange, and dissemination through guidelines, publications, online resources and scientific events."[53] Because it reaches across sectors, involves all interested stakeholders, and has broad application, it is seen as *the* resource for non-animal testing issues, although it does support animal experiments where justification is "scientifically compelling." One of its biggest goals in the short term is to minimize animal testing with the eventual goal of moving toward full replacement; however, there is recognition that animal testing presently has some utility. NC3Rs annual budget is approximately £7 million and it receives most of its funding from the Department for Business, Innovation and Skills via the Medical Research Council and the Biotechnology and Biological Sciences Research Council, and the Home Office. It also receives funding for specific programs from the nonprofits, industry, and other research funders. Some notable funders include GlaxoSmithKline, SCJohnson, Shell, Dow Chemical, and Unilever.[54]

Because FDA-regulated products make up about 25 cents of every dollar spent in the U.S., FDA touches American lives directly.[55] The FDA's budget for 2016 is ~$4.9

[53] National Centre for the Refinement, Replacement & Reduction of Animals in Research, "Who we are and what we do," http://nc3rs.org.uk/who-we-are-and-what-we-do.
[54] National Centre for the Refinement, Replacement & Reduction of Animals in Research, "Our funding," http://nc3rs.org.uk/about-us/funders
[55] U.S. Food and Drug Administration, "Executive Summary: Strategic Plan for Regulatory Science," 2013, http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm268095.htm.

billion and ~$2 billion of that is generated from pharmaceutical user fees.[56] FDA is known for being one of the more conservative regulatory agencies, as opposed to EPA which is more progressive in its institutional thinking. This may be in part due to the fact that it regulates many high-stakes products, like drugs, as well as conservative industries, like cosmetics. One of the largest cosmetic trade groups is the Personal Care Product Council (PCPC), which represents large national and global cosmetics companies. The history section of PCPC's website starts in the 1880's to give a sense of how old an institution it is. Its members comprise all the national cosmetic and personal care product companies in homes across the country and it has a vested interest in seeing animal tests continue despite the fact that globally the trend is to move away from animal experiments for cosmetics.[57] After having spoken directly to many PCPC member companies it is clear that the interest lays in cosmetic companies' ability to "innovate," and the expectation with new cosmetic chemicals is a safety profile dependent on animal data for FDA. FDA does not require the use of animal data for cosmetics. In fact, there is no law in the U.S that mandates animal testing, but large cosmetic companies like to conduct the animal tests to protect themselves in the event of a legal battle and to prove to the FDA that their ingredients and products are safe. Animal protection advocates have spoken repeatedly with PCPC on the value of non-animal testing methods but there is not an institutional desire to move away from the current heavy reliance on animal tests.

[56] U.S. Department of Health & Human Services, "HHS FY2016 Budget in Brief," 2015, http://www.hhs.gov/about/budget/budget-in-brief/fda/.
[57] Ibid.

Other industry trade groups that are not supportive of non-animal testing methods are the National Association for Biomedical Research (NABR) and the Pharmaceutical Research and Manufacturers of America (PhRMA). NABR primarily represents the interests of pharmaceutical and biotechnology companies as well as medical, research, and veterinary institutions. NABR uses lobbying and other government affairs strategies to communicate the value of animal experiments at all levels of the federal government. Having been established in 1979 it represents more than 350 members.[58] It spends about $1.5 million a year.[59] PhRMA is a similar group that focuses on the policy issues the pharmaceutical industry faces. PhRMA does not address the issue of non-animal testing methods but it also does not come out against them. It is seen as the go-to resource for public policy related issues for the pharmaceutical industry and is one of the largest and most influential lobbying powerhouses in Washington, DC, representing 48 pharmaceutical companies.[60] In 2010 it spent nearly $22 million in lobbying expenses and recently tweeted, "The biopharma industry spends more on R&D than the entire NIH operating budget."[61] It is the wealthiest of all the stakeholders discussed here.

Some of the least endowed of the stakeholders are the animal protection groups. The three organizations working to address the use of animals in experiments

[58] National Association for Biomedical Research, "Membership," 2015, http://www.nabr.org/about/membership-2/.
[59] ProPublica, "National Association for Biomedical Research," 2016, https://projects.propublica.org/nonprofits/organizations/42688181.
[60] SourceWatch, "Pharmaceutical Research and Manufacturers of America," 2012, http://www.sourcewatch.org/index.php/Pharmaceutical_Research_and_Manufacturers_of_America.
[61] Sarah Ferris, "Facing bipartisan attacks, PhRMA goes on offensive," The Hill, 2015, http://thehill.com/policy/healthcare/259050-facing-bipartisan-attacks-phrma-goes-on-offensive.

are People for the Ethical Treatment of Animals (PETA), the Humane Society of the United States (including its Legislative Fund, and international body (HSUS/HSLF/HSI), and the Physicians Committee for Responsible Medicine (PCRM). PETA has a budget of $45 million,[62] the HSUS family has a budget ~$180 million,[63] and PCRM's budget is ~$13 million a year.[64] They all have shifted from employing activists and campaigners to primarily employing scientists. They work to impact the status quo by using science as their tool. They also work collaboratively with scientists and government agencies to bring about change. For example, last year PCRM hosted a workshop with NIH on alternative testing methods and more than 500 scientific experts attended.[65] The animal protection groups are fueled by the ethics and that is what drives the sense of urgency, but they use science in all the talking points, understanding that the issue will only move forward when there is a collective scientific acknowledgement that non-animal testing methods are the best way to obtain information for human health and the environment.

Policy Proposal

Shifting to modern, non-animal testing methods will require intention and a shift in thinking and approach. To help facilitate this, the proposal set forth is to establish a nonprofit organization with the sole function of collaborating with scientists and

[62] People for the Ethical Treatment of Animals, "2015 Financial Statement," 2015, http://www.peta.org/about-peta/learn-about-peta/financial-report/.
[63] The Humane Society of the United States, "Annual Report 2015," 2015, http://www.humanesociety.org/about/overview/financials/hsus-annual-report-2015.html?credit=web_id86463704.
[64] Physicians Committee for Responsible Medicine, "Form 990," 2014, http://www.pcrm.org/sites/default/files/physicians-committee-irs-form-990-fye-2015.pdf.
[65] Physicians Committee for Responsible Medicine, "Physicians Committee Sponsors Landmark Nonanimal Toxicology Workshop," 2014, http://www.pcrm.org/media/online/oct2014/physicians-committee-sponsors-landmark-nonanimal

organizations across the life sciences from industry, academia, funders, and regulatory authorities. The goal is to help manifest the 3Rs vision in the U.S., bringing the number of animals used in toxicological experiments down while improving public health. This will be achieved by creating a coalition of stakeholders including industry and academia to help develop non-animal testing methods and create a space for scientists to discuss challenges and ways to overcome them. The initial step will be for all involved (across sectors) to sign a pledge with the stated intention. Then a steering committee will be developed to outline the challenges and develop a workshop or conference to address these. An outcome of this initial physical event will be a scientific paper in a reputable journal to help establish legitimacy to the mission and garner more visibility. As the organization grows, regulators will be brought in to help understand what challenges they face in understanding non-animal testing methods and educate them on how the modern testing methods work so they are more comfortable accepting data from these techniques. This proposal is similar to the successful NC3Rs center in the UK. Similar to the NC3Rs, the short-term goals would be to minimize animal tests wherever possible, with the understanding that animal testing may be needed in certain instances, and the long term goal of fully replacing the use of animals with non-animal technology.

Policy Authorization Tool

Federal law stipulates that tax deductions may be provided to nonprofit organizations that qualify under section 501(c)(3) of the Internal Revenue Code. In order

to apply for this status, the entity must apply to the Internal Revenue Service (IRS).[66] The organization would start by creating a nonprofit corporation and file an Articles of Incorporation form. Then, to obtain the 501(c)(3) status the nonprofit will have to file IRS form 1023. It may take many months, if not more than a year, to officially be granted status by the government. Before the paperwork is filed it is important to ensure a board of directors is in place, bylaws are created, and the appropriate legal structure has been selected. In addition, an Employer Identification Number is needed by completing IRS From SS-4.[67]

Policy Implementation Tool

Creating a nonprofit organization that reaches across industries and stakeholders will create opportunities and space for collaboration. The model will be adapted from the NC3Rs in the UK where they dedicate all their resources to the 3Rs. NC3Rs focuses their programs in three areas: 1) funding research and early career development, 2) supporting commercialization and facilitating technology partnerships, and 3) providing an evidence base for policy changes, practice and regulation. This is carried out through data sharing, knowledge exchange, and dissemination through guidelines, publications, online resources, and scientific events.[68] A similar approach is needed in the U.S. and nothing like this exists. Currently, animal protection organizations hold workshops and seminars semi-regularly to achieve some of these goals, but there is no cohesive effort

[66] Internal Revenue Service, "Application Process," 2016, https://www.irs.gov/Charities-&-Non-Profits/Application-Process.
[67] Cullinane Law Group, "How to Set Up a Non Profit with 501(c)3 status," 2014, http://cullinanelaw.com/how-to-set-up-a-non-profit-with-501c3-status/.
[68] National Centre for the Refinement, Replacement & Reduction of Animals in Research, "About Us," http://nc3rs.org.uk/about-us.

to implement the 3Rs in the scientific community (in the U.S.). Modernizing testing methods is a public health issue and should be treated as such – not simply an animal protection issue.

Academia has the incentive to work collaboratively to advance the scientific research and propel the state-of-the-art forward. Industry has an incentive to work in this type of space to ensure that the best testing methods are used for safer products and to bring more products onto the market quicker. An organization like this could also serve as a space to share information from regulators to the industry at-large in a quick and efficient manner – the current method is for regulators to disseminate viewpoints individually with companies, causing confusion and lack of clarity.

As previously stated, NC3Rs annual budget is approximately £7 million. However, to get something off the ground in the U.S. considerably less would be needed. As the organization grows it could increase its budget and the hope is that industry partners would contribute to this effort as they have with NC3Rs. The requested preliminary budget, for the first year only, would account for staff time of a director with an advanced degree to run the organization at $120,000 including benefits, two coordinators, one with a scientific background, would be needed at $60,000 including benefits. A fundraiser will be necessary at a salary of $80,000, a lawyer at $90,000, and an accountant at $70,000, including benefits. A small office space in the DC metro area will cost ~$4,000 a month for six individuals. Hiring strategic consultants will also run approximately $15,000. The first year will require a lot of initial face-to-face conversations with potential collaborators and stakeholders necessitating a travel

budget of approximately $50,000. Funds to create a website, initial set up of office materials, software, and other miscellaneous items will run ~$20,000. With all this, the request for $633,000 from the Michelson Medical Research Foundation has been placed.

Policy Analysis

There are a number of opportunities and challenges with the policy proposal set forth in this decision memorandum.

Opportunities

Many scientists agree that a policy solution is needed for the problem at play.[69] However, there are copious hurdles and challenges, but also opportunities to think and act creatively. One of the biggest advantages of seeing this nonprofit organization come to fruition is the sheer fact that nothing like this exists in the U.S. Different methods and tactics are often needed to address large, complex issues such as this one. Creating a space where dedicated time and resources are devoted to thinking through the issue of how to advance science to move beyond animals for public health is needed. There is value in actually having a *space* like this because when a group of individuals are tasked with the responsibility of seeing a specific mission move forward it helps make it a reality. Currently, the onus is only on the animal protection groups who are motivated by the ethical ramifications of animal testing, but there is no concerted scientific push and this policy proposal would help shift that.

[69] National Research Council, "Toxicity Testing in the 21st Century: A Vision and Strategy," National Academy of Sciences, 2007, http://www.nap.edu/catalog/11970/toxicity-testing-in-the-21st-century-a-vision-and-a.

There is also great growth potential with this organization due to the fact that industry is already supporting efforts like this in the UK. If this organization grows the way NC3Rs has, many potential opportunities could become reality, including the creation of an actual lab where bench scientists work through challenges collaboratively. If such a lab were to be created, workshops could be hosted on the technical details of non-animal testing methods. These workshops could be geared toward young scientists and those unfamiliar with non-animal test methods. It has been shown (earlier in this memo) that a continued reliance on animals is adversely affecting the public and an organization like this could save human lives by advancing the scientific field. If and when more sophisticated methods are developed and used (and this organization would help disseminate that information) the potential to save human lives will increase. Merck's senior vice president Dr. David Nicholson gives an example: "The limitations of animals as stand-ins for human patients are a major reason [for drugs to fail]. Animal disease doesn't faithfully replicate asthma, for instance. The condition is uniquely human...and animal models can't capture the constriction of airways and all of the other characteristics of the disease. We have found great mechanisms that can control asthma in animals and most of them have failed in humans."[70] However, an article in *Drug Discovery Today* (a review journal covering the issues of preclinical drug discovery) helps find the solution: "Many scientists believe that progress in this field [asthma research] rests on linking disciplines to make research

[70] Jonathan Rockoff, "Forget Lab Rats: Testing Asthma Drugs on a Microchip," Wall Street Journal, 2013, http://www.wsj.com/articles/SB10001424127887324049504578545154163286708.

directly translatable from the bench to the clinic; a '21st-century' scientific approach to address age-old questions."[71]

Because well-endowed and established industries will be impacted by an organization like this, contributions from them will go a long way at a small nonprofit organization. The goal of the first year will be to bring a reputable scientific leader to help shape the conversation, create a scientific advisory board, and invite industry collaborators. It is expected that industry will contribute to this effort. While it is well documented how industry collaborates with NC3Rs it is also worth noting that in the U.S., a number of entities came together to create the American Society for Cellular and Computational Toxicology (ASCCT). ASCCT is a scientific society dedicated to the promotion of toxicology testing (in the chemicals and cosmetics sectors) to reduce and replace the use of animals.[72] Founding members, which included financial investment, include: Avon, Clorox, Colgate-Palmolive, SC Johnson, and the Research Institute for Fragrance Materials. While ASCCT is much narrower in scope than this organization aims to be, this example illustrates that there is corporate interest in the U.S. to contribute to similar organizations with a shared goal.

Another key advantage to creating an organization like this is because there is a model in the UK that has been thriving for more than 10 years. It is always hard to judge whether an organization is working as effectively as its intended goal but one metric that shows NC3Rs success is its publication and citation rate. NC3Rs papers are more

[71] G.L. Buckland, "Harnessing opportunities in non-animal asthma research for a 21st-century science," Drug Discovery Today, 2011, http://www.ncbi.nlm.nih.gov/pubmed/21875684.
[72] American Society for Cellular and Computational Toxicology, http://www.ascctox.org/about.

heavily cited than the world average.[73] Publications are one of the key ways in which scientists contribute to the field. Being published is a challenge because the peer-review process is difficult but having your work read by others is another obstacle. The work coming out of the NC3Rs is known for being high quality and advancing the challenges faced by the community, so to be able to say that their work is highly cited, more than other works elsewhere in the world, is a quantifiable measure of success.

Finally, while this is not the goal, nor is it the theme of the memo, it should be noted that one of the advantages of having an organization like this is it helps solve the ethical issues associated with experimentation. Tens, if not hundreds of millions of animals are used every year in laboratories across the U.S. Their lives are spent in physical and emotional/mental distress. They experience prolonged pain without relief and are unable to exhibit their natural behaviors or live free as they would outside of the laboratory. Studies continue to show how physically and emotionally capable all animals are. Further, mice and rats make up ~95 percent of the animals used in experiments, but they are a lot more like humans than one might think.[74] Rats not only feel pain but they also feel joy. In fact, rats laugh when tickled.[75] They also feel each other's pain (or at least see it in each other's faces),[76] and rats can tell the difference

[73] Vicky Robinson, "Information to Apply the 3R's – the NC3Rs Approach," National Centre for the Refinement, Replacement & Reduction of Animals in Research, http://ec.europa.eu/environment/chemicals/lab_animals/pdf/NC3Rs_Robinson.pdf.
[74] American Anti-Vivisection Society, "Mice and Rats," 2016 http://aavs.org/animals-science/animals-used/mice-rats/.
[75] Jacqueline Howard, "Rats Laugh When Tickled, Scientists Say," Huffington Post, 2012, http://www.huffingtonpost.com/2012/06/26/rats-study-animals-laugh-tickled-video_n_1627632.html.
[76] Virginia Morell, "Rats see the pain in other rats' faces," Science, 2015, http://www.sciencemag.org/news/2015/03/rats-see-pain-other-rats-faces.

between a Picasso and a Renoir painting.[77] Male mice break out into song when they want to woo their potential mates.[78] The serenade is too high-pitched to be heard by humans, but scientists recently lowered the pitch to make it audible to the human ear. What else do we not know about the rich emotional lives of these animals? Do we have an ethical imperative to consider their lives and pain when conducting experiments? This policy proposal will help address these issues, albeit inadvertently. Still, it is an unintended positive byproduct.

Challenges

As with all ideas, there are a number of challenges with this policy proposal, the biggest one being that without direct involvement from the government the utility of this organization might be in question. High-level strategic planning is needed to implement the vision of the 3Rs in the U.S. A primary reason NC3Rs is so successful is because it is housed under the Home Office and receives government funding. Because the government is intricately tied to the NC3Rs in the UK it provides an unofficial stamp of approval, creating an aura of legitimacy that this U.S. based organization would not have. Another challenge facing industry in the U.S. is that government regulators advise companies based on the regulator's individual backgrounds and not on unified standards set forth by the agencies. For example, the FDA does not have official guidance for the pharmaceutical industry on LD_{50} studies. This translates to confusion amongst regulators who need to uphold the safety standard set forth by the law, so

[77] Shigeru Watanabe, "Preference for and Discrimination of Paintings by Mice," PLoS One, 2013, http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0065335.
[78] Duke Today, "Mice Sing like Songbirds to Woo Mates," 2015, http://today.duke.edu/2015/04/mousesong.

some regulators ask companies to provide this data and some do not. Part of this problem is that regulators receive different training at the academic level so they have varying levels of comfort and knowledge with non-animal technology. This creates a culture in industry whereby companies "front-load" animal data to ensure a smooth regulatory process even if that animal data is not needed or useful. While solving this problem is complex, a public-private partnership might be better suited to address these types of problems and not a nonprofit organization, which will be limited in what it can achieve by way of regulatory capture. Additionally, without government involvement the organization will have a harder time soliciting industry cooperation. Continuing on this point, regulators are beholden to the existing laws and regulations so there may be a need to change these policies at a federal level, something this nonprofit is not set up to do at this time.

Another reason why a public-private partnership would be advantageous would be to help fund scientific research and initiatives. Five years after NC3Rs was founded the government decided to substantially increase the amount of grants it would allow NC3Rs to give based on its record of success.[79] The project grants range from studentships, to pilot studies, to fellowships, to post-doc opportunities. This investment by the government illustrates a clear and consistent impetus to move toward non-animal technology. In addition to the direct grants NC3Rs gives, it has also been able to develop a funding competition and technology partnering hub called CRACK IT. The goal

[79] UK Government, "Working to reduce the Use of Animals in Research," 2014, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/277942/bis-14-589-working-to-reduce-the-use-of_animals-in-research.pdf.

of this new effort is to "accelerate the development, application and commercialization of technologies with 3Rs potential as they emerge from the research base."[80] Efforts like this are made possible because of the investment the government has made in advancing non-animal technology. Without that level of involvement in the U.S. the outcomes may not be as valuable as one would hope.

Another key issue is whether this organization is too broad focusing on the entire field of toxicology rather than specific challenges brought forth by the pharmaceutical or chemical industries. To elaborate, pharmaceuticals are meant to be biologically active and have a treating or curing effect. Chemicals on the other hand, are not designed to be biologically active and if they impact human health it is inadvertent. Because of these fundamental differences in chemistry, the types of problems and challenges, as well as solutions and alternatives, testing methods will vary significantly. The challenges each sector faces are different, potentially necessitating different solutions. This new organization may be too broad to capture these nuances. Many times organizations that cover a lot of ground start off focused and then expand as budgets grow. There are reasons why starting with a multi-industry focus is a good approach but it could also prove to be a challenge if resources, including funding and personnel, are limited. It is risky either way; if the organization starts out too focused it may never expand to cover the totality of the issue at hand. Alternately, if the organization tries to cover too much ground at the outset it may doom itself by failing to get off the ground. Leadership and vision will be key and that may prove to be another challenge. Finding someone who

[80] Crack It, http://www.crackit.org.uk/.

has a good base of experience as well as a broad skill set is difficult. Someone who comes to mind is the current director of NCATS, Dr. Chris Austin. He currently leads government funded translational research but he also has private sector experience. He founded the National Chemical Genomics Center so he understands what is involved in getting something started and is also well respected by colleagues. Few other people fit these types of credentials and finding the right leader will prove to be challenging.

Another challenge will be getting stakeholders to agree on what the short-term goals should be. The "3Rs" mean different things to different people. Some believe that full replacement should be the goal and nothing less. Some believe that refinement should be the first step, then reduction, then refinement, and that projects should be prioritized accordingly. While this discrepancy may sound small it actually reflects a fundamental difference in overall philosophy and vision. If the mission and vision cannot be agreed upon then there is no basis for an organization. The NC3Rs has decided to place emphasis on replacement methods while acknowledging that there are opportunities for reduction and refinement methods right now and that they should be explored and funded. However, I would expect this to be a point of contention in the U.S. because so many people have strongly held beliefs around this issue.

Finally, it should be noted that ethics contribute to this challenge, albeit in a different way than in the opportunity section. A major consideration of the mission and vision of this organization will be whether to publicly highlight the ethical issues with animal experimentation. Often scientists do not want to engage in philosophical or ethical issues, but they will surely arise if an organization like this is developed. There

will need to be clear and consistent agreement amongst the board and staff as to how the ethical considerations will be woven into the discussion of the formation of this organization. It is clear that ethics will not be the focus of this organization but how those issues will be dealt with may turn out to be a challenge because scientists have varying levels of comfort with the topic.

Political Analysis

There are a number of political strengths and weaknesses associated with this proposal. The strengths fall under two broad categories: public support and growing interest from both Republicans and Democrats. Weaknesses are the lack of a majority in Congress supporting a ban and the strong influence of certain groups that will likely oppose this proposal.

Strengths

For more than a century activists have tried to shift public opinion about animal experiments due to the cruelty inflicted on the animals.[81] However, the ethical considerations surrounding the use of animals in laboratories are starting to gain support in public opinion polls. In 2003 Gallup asked Americans their views about animals in laboratories and they found that 35 percent of Americans supported a ban on animal experiments for medical research. More recently, Gallup conducted a different poll in 2015 showing that the use of animals in experiments is of increasing importance for many Americans, with 67% of Americans saying they were very or somewhat

[81] Lily Santoro, "Our History," American Anti-Vivisection Society, 2016, http://aavs.org/about/history/.

concerned about the use of animals used in research.[82] [83] While these results do not directly correlate to each other it shows that in recent decades Americans are aware and concerned with the use of animals in laboratories broadly.

More specifically, in 2011 PCRM commissioned ORC International to conduct a national survey asking individuals about their views on the use of animals in cosmetics testing. They found that 72 percent of respondents agreed that testing cosmetics on animals is unethical. An even higher percentage—78 percent—of respondents agreed that the development of alternatives to animal testing for cosmetics testing is important. Finally, 61 percent of respondents said that cosmetics and personal care product companies should not be allowed to test products on animals.[84] Humane Society International (HSI) conducted a similar poll recently but on a global scale, they published the results this past January. HSI found that 8 out of 10 Canadians support a national cosmetics animal testing ban, 7 out of 10 South Koreans support a national animal testing ban for cosmetics, two out of three Brazilians support a national ban, and nearly 90 percent of people in Japan responded that "I don't want manufacturers to use ingredients in cosmetics whose safety cannot be determined unless they are tested on animals." And 69.2 percent of Taiwanese consumers want to see cosmetics animal

[82] Rebecca Riffkin, "In U.S., More Say Animals Should Have Same Rights as People," Gallup, 2015, http://www.gallup.com/poll/183275/say-animals-rights-people.aspx.
[83] David Moore, "Public Lukewarm on Animal Rights," Gallup, 2003, http://www.gallup.com/poll/8461/public-lukewarm-animal-rights.aspx.
[84] Physicians Committee for Responsible Medicine, "More Than a Makeup Trend: New Survey Shows 72 percent of Americans Oppose Testing Cosmetics Products on Animals," 2011, http://www.pcrm.org/research/animaltestalt/cosmetics/americans-oppose-testing-cosmetics-on-animals

testing banned.[85] These data show that there is a strong desire among the general public both nationally and internationally to see a shift away from animals used in laboratories.

Support among elected officials is harder to quantify than polling data but evidence suggests movement on this front is possible. The issue of cosmetics testing is seen as "low-hanging fruit" in the animal protection community because public support for the cause is greater than other experimentation issues. Although there is no real traction for this issue at the legislative level there seems to be an intuitive sense from policy makers that it is ethically questionable whether an animal should suffer and die for the next shade of lipstick or mascara. In the past two Congressional sessions different Members of Congress have introduced and supported the Humane Cosmetics Act, which would ban the testing and sale of animal tested cosmetics. Rep. James Moran (D-VA) first introduced the bill in 2014 and he was able to secure 54 cosponsors by the end of the session.[86] In 2015, Rep. Martha McSally, a Republican from Arizona's second district, introduced the same bill due to Rep. Moran's retirement. The bill currently has 154 cosponsors with much more support from Republicans than the previous session.[87]

The issue of animal testing is one that is seemingly bipartisan and a timely example of this is with TSCA reform. As previously stated, the conference committee is currently working out the details between the Senate and House versions of their

[85] Humane Society International, "Global Polls Reveal Consumers Worldwide Want an End to Animal Testing for Cosmetics," 2016, http://www.hsi.org/news/news/2016/01/global_cosmetics_polling_012716.html.
[86] United States Congress, "H.R.4148 – Humane Cosmetics Act," 2014, https://www.congress.gov/bill/113th-congress/house-bill/4148.
[87] United States Congress, "H.R.2858 – Humane Cosmetics Act," 2015, https://www.congress.gov/bill/114th-congress/house-bill/2858/cosponsors.

respective chemical reform bills but the issue of animal testing has had a significant amount of support from Republicans throughout the process. The main reason for this support is because animal tests are expensive and often a regulatory burden on industry. In fact, the animal protection community was able to put together joint principles on animal experimentation back in 2011 because both sides agreed that animal experiments are not useful. Industry claims they are too expensive and the animal protection community is motivated by ethics. In the end the animal protection community was able to join a number of public health organizations, trade unions, environmental organizations, and industry in backing the Senate TSCA reform bill, which passed out of the Senate last December by unanimous consent.[88]

It is worth noting that political will is also international. In the UK the scientific community is motivated by ethics and they are not afraid to discuss the ethical issues publicly. In fact, in 2014 a UK-based "delivery plan" titled *Working to Reduce the Use of Animals in Scientific Research* was developed in collaboration between the Home Office Animals in Science Regulation Unit, the Department for Business, Innovation and Skills and Government Office for Science. It reflects significant input from other government departments including the Department of Health, the Department for Environment, Food and Rural Affairs, the Food Standards Agency, and the Foreign & Commonwealth Office, as well as a number of government agencies including Public Health England, the Medicines and Healthcare Products Regulatory Agency, the Veterinary Medicines Directorate, the Animal Health & Veterinary Laboratories Agency, the Food &

[88] Senator Tom Udall, "Chemical Safety," http://www.tomudall.senate.gov/chemicalsafety/.

Environment Research Agency, the Centre for Environment, Fisheries & Aquaculture Science, and the Health & Safety Executive.[89] Based on the names alone one can see a significant effort by the part of the UK government to reduce the use of animals in laboratories and that there is recognition that this issue crosses many sectors. While it is true that there are many differences between the U.S. and the UK, it is worth looking at the global community as an example that there is appetite for a nonprofit organization such as the one proposed in this memorandum.

Weaknesses

Although support has grown in Congress, this proposal is still far short of the majority needed for passage. In order to more closely mirror some of the success the NC3Rs has seen involvement from government agencies would be necessary. There is value in the creation of a 501(c)(3) because the organization could make statements and proposals to help push the field (more than one that is connected to the government), but there are also significant limitations. Without government involvement at the institutional level there would not be a clear commitment on the direction of the state of science. Said another way, government should be the leader on this issue because most of the regulatory testing occurs for government review. Without clear intent by way of the government, industry and other stakeholders can get lost in whether animals should be used or whether certain "lower" animals should be used versus those "higher" on the evolutionary ladder. Having government involvement would also help

[89] UK Government, "Working to reduce the Use of Animals in Research," 2014, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/277942/bis-14-589-working-to-reduce-the-use-of_animals-in-research.pdf.

wield influence – and demonstrate that this issue is a priority – to the academic sector because it would provide a clear signal that development of non-animal testing methods should be developed. In fact, this is what was seen with the TT21C report. The field of toxicology was able to really value what many scientists had been saying (that a shift away from animals was necessary) only after the NAS came out with its report and the EPA built programs around those findings. Finally, government involvement could also spur grants and other sources of funds for non-animal test method development, as is currently the case with NC3Rs. This lack of political support is part a result of congressional gridlock. A potential solution to this issue would be for Congress to charter and call for the creation of a 501(c)(3) as they did with the Reagan-Udall Foundation for the FDA to help solve some of the policy and implementation issues faced by the agency.

Another hurdle is the number of politically powerful groups opposed to this proposal. Currently, the largest organized group of supporters for this proposal is the animal protection community. In addition, there are a number of respected scientists across industry and government who believe in this mission but there is no unified group. However, there are a number of industries, organizations, and lobbyists who are financially invested in animal experiments. NABR was mentioned earlier because it has a strong presence on the Hill, but other groups such as Federation of American Societies for Experimental Biology—the largest coalition of biomedical researchers—is heavily funded by animal experiments, as is the Foundation for Biomedical Research whose sole goal is to promote animal-based research to the public. In addition to organized groups

such as these, there are also contract research organizations (CROs). CROs are labs that conduct outsourced animal tests for companies across all industries. They are well funded and heavily interested in seeing animal experiments continue because they exist solely to conduct animal experiments. CROs help fund some of the organizations listed above.[90] Companies and organizations like this view proposals such as this one as an unnecessary way to slow down research. They claim that 3Rs are already built into protocols in laboratories across the nation so unifying an effort like this is not a good use of resources or time.

Recommendation

There are significant pros and cons to this proposal. One of the most significant cons is the fact that because this proposal is set out to create a nonprofit organization, government will not be involved thereby making it harder to solicit industry cooperation. Related to this point is the fact that regulators are only going to change their practices once regulations and laws are changed. This nonprofit will not be able to solve those problems because 501(c)3's are not able to heavily engage in Congressional lobbying (it can within certain restrictive parameters). Additionally, because this organization will not be connected to the government it will be unable to give government sponsored grants, which would help provide legitimacy to the concept that the development of alternatives is necessary. Finally, if this nonprofit organization were to come to fruition it would make it more difficult for a similar 501(c)3 created by

[90] Federation of American Societies for Experimental Biology, "Federal Funding," 2016, https://www.faseb.org/Portals/2/PDFs/opa/2015/FASEB%20Federal%20Funding%20Report%20FY%202016.pdf

Congress or a public-private partnership to be created and one of these options may be a more appropriate tool for solving the problem outlined in this proposal.

With all of this said it is recommend that the Michelson Medical Research Foundation support this proposal. Momentum is needed to address the public health ramifications of continued reliance on animal experiments and the time is now to tackle the problem of unreliable testing. No similar proposals currently exist in the U.S. Pressure is needed in the scientific community and having an organization put the onus on scientists would help move this issue beyond animal protection advocates. Additionally, one never knows what organizations can turn into. There is value in having an actual space to tackle these complex issues. There may be an opportunity down the line to create a lobbying force to address the political issues at hand, or maybe a laboratory could be funded in which scientists work on the bench to solve problems. The growth potential is tremendous and none of it will be realized unless we dig in and get started. Trying to find the perfect solution from the outset may not be realistic, sometimes the best way to start addressing an issue is to simply jump in. Waiting for a political opening through a government created 501(c)3 or a public-private partnership may take decades especially based on the political gridlock witnessed today. Too many lives—both human and non-human—are at stake to wait for an opportunity at the Congressional level, the downside of inaction may be greater than the risk of starting now.

The funding issue is a legitimate con, while government grants may be the best way to offer support to scientists looking to develop alternative testing methods, a

nonprofit organization may be able to galvanize financial support from multiple sources (foundations, charities, individuals, etc.). Government-funded grants help give legitimacy to the issue but non-government funded grants may help create public support and awareness, as well as potentially secure more money if a development team was tasked solely with this project. Appropriations are subject to debate nearly every year and a nonprofit would be shielded from that tumultuous, political rollercoaster. Therefore a nonprofit funding mechanism may actually be a solution to what was originally discussed as a con.

While the final two reasons to support this proposal are "soft" issues they are worth serious attention. Firstly, it should be noted that the public supports efforts to minimize animal experiments. More and more the public is becoming aware of the suffering that animals experience in labs. Animal protection advocates continue to push the public to be uncomfortable with what happens to animals behind closed doors and awareness is gaining ground as outlined in the political section. Secondly, while ethics were not the focus of the paper it is necessary to note that any type of effort to alleviate the pain, suffering, and death of hundreds of millions of animals is worth exploring. Animals in experiments live their entire lives without seeing sunlight or grass. They never get to feel joy or exhibit their natural behaviors. They are social creatures separated from their families, living lives in solitary confinement, and tortured by their experimenters almost daily. They are rarely given pain relief, even for some of the most invasive procedures. They long to live free just like any human. The most disturbing aspect of their suffering is that it provides questionable results for the human

population. It is precisely because animal-derived data does not give human-relevant information *and* because of the suffering involved that we must do everything in our power to help change the current paradigm and move towards a safer and less cruel world.

CURRICULUM VITA

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